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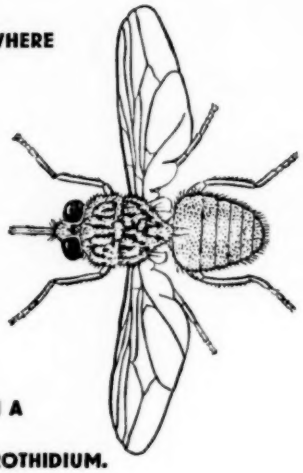

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No. 33 AUGUST 16th, 1958 Vol. 70

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Immunity in Trypanosomiasis and its Effect on Chemotherapy*

BY

M. A. SOLTYS

University of Cambridge Department of Animal Pathology,

Infection must be considered as a struggle between two organisms, the parasite and its host . . . This struggle brings about adaptations on both sides.—METCHNIKOFF, 1891.

THE literature concerning immunity in trypanosomiasis which has appeared during the last 50 years consists mainly of reports on investigations aimed at developing serological tests which may be applied to the diagnosis of various trypanosome infections. The work on acquired immunity has been very scanty and most of the published work consists either of field observations or laboratory studies in infected experimental animals cured by drugs and based on crude immunological tests. In evaluating these experiments it was noted that one of the serious handicaps to studies of the problem of immunity was the lack of a suitable method for the detection of protective antibody. In this communication, I shall describe the methods by which neutralising antibody or protective antibody can be demonstrated in the serum of animals that were either infected by virulent trypanosomes or else hyperimmunised by repeated inoculations of dead trypanosomes, and the results of experiments, which may help in the understanding of some of the immunological problems in trypanosomiasis and also the effect of immunity on chemotherapy.

Neutralisation Test and the Development of Antibody-resistant Strains

Neutralisation of trypanosomes by sera of goats and sheep, which had recovered from nagana (*Trypanosoma brucei* infection) was first reported by Mesnil and Brimont in 1909 and was later confirmed by other workers. Recently, Soltys (1957), studying the presence of neutralising antibody against trypanosomes, demonstrated that sera of rabbits infected with *T. brucei* are able to neutralise this organism in dilutions of 1:320 and higher, while sera of these animals prior to infection failed to show any neutralisation even in dilution of 1:10. The technique of the neutralisation test used was similar to that used for the neutralisation of viruses and has been described in detail by Soltys (1957).

The neutralising antibodies were demonstrated in infected rabbits after 5 days and gradually increased to a peak within 28 days at which time they were inoculated with suramin*. The maximum titre persisted for 98 days and then gradually decreased and disappeared after 154 days.

Neutralising antibody in the same titre as in infected rabbits was also demonstrated in rabbits immunised with dead trypanosomes. This indicates that immunity against trypanosomes develops in much the same way as in bacterial infections and does not necessarily require living trypanosomes. The generally accepted view that in African trypanosomiasis, acquired immunity is always of the nature of "premunition" requiring the persistence of the living agent is, therefore, fallacious, and has been accepted without proper experimental evidence. It seems that the term "premunition" was used by various workers, because they found trypanosomes circulating in the animal body in the presence of antibodies. These observations also led to studies on antigenic variations. This subject is discussed by Soltys (1957). Ritz (1916), and other workers concluded that trypanosomes must change antigenically and produce successions of immunologically different varieties. In order to find if the capacity of

* Paper given at a Symposium on Immunology organised by the Scottish Branch of the Association of Veterinary Teachers and Research Workers on May 10th, 1958, in Glasgow.

* Bayer 205.

trypanosomes to vary serologically is inexhaustible, the following experiment was carried out. The parent strain of *T. brucei 0.* which had been maintained in mice was continued in passage through mice and the same original strain was passaged through rabbits. Sera from the rabbits during the passage of the strain were collected and examined by the neutralisation test against the strain passaged through mice and against the strain isolated from rabbits at the same time when the serum was collected. The results of this experiment are shown in Table I.

Table I indicates that sera of rabbits infected with *T. brucei 0.* passaged through rabbits were able to neutralise only "M" variant of *T. brucei 0.* which was passaged through mice and not exposed to antibodies, but failed to neutralise "R" variant of *T. brucei 0.* after passaged through rabbits and exposed to antibodies. It appears from these experiments that trypanosomes which were passaged through rabbits and consequently exposed to antibodies formed some kind of defensive mechanism or compound which protected them against antibodies and allowed them to live in its presence.

It would be most interesting to find out whether the protective mechanism of antibody tolerant strains is of capsular nature, or of enzymatic nature. Studies on this line of thought are being pursued. I wonder whether bacteria produce defensive mechanisms similar to those of trypanosomes and therefore when we fail to demonstrate neutralising antibody in bacterial infections we cannot conclude that neutralising antibody is not produced? There is no doubt that we have to study more, not only how the host tolerates the parasite, but also how the parasite tolerates the host. Further observations have shown that a variant of *T. brucei 0.*, which was antibody tolerant, increased its pathogenicity not only to rabbits but also to guinea-pigs, which were fairly resistant to the same strain which was antibody sensitive.

Sensitivity of the Antibody-resistant Variant to Chemotherapeutic Drugs

It was also found that *T. brucei 0.* which became antibody resistant after passage through rabbits, was more resistant to suramin than the same strain passaged through mice which was antibody sensitive. The latter observations suggested further studies on the sensitivity of these two variants of *T. brucei 0.* to chemotherapeutic drugs. In these studies Soltys (1958) has shown that *T. brucei 0.* passaged through rabbits was less sensitive to suramin and antrycide than the same strain, which had been passaged through mice. The results of these experiments are summarised in Table II.

The difference in sensitivity to suramin and antrycide between the antibody sensitive strain (mouse strain) and the antibody resistant strain (rabbit strain) clearly indicates that in chemotherapy and chemoprophylaxis with trypanostatic agents, the natural mechanism of defence and immune bodies act together with the drugs. These experiments also suggest that antibody resistant strains which require more drugs may lead to the development of drug resistant strains.

TABLE I

SENSITIVITY OF *T. brucei O.* PASSAGED THROUGH TWO DIFFERENT SPECIES OF ANIMALS TO NEUTRALISING ANTIBODY.

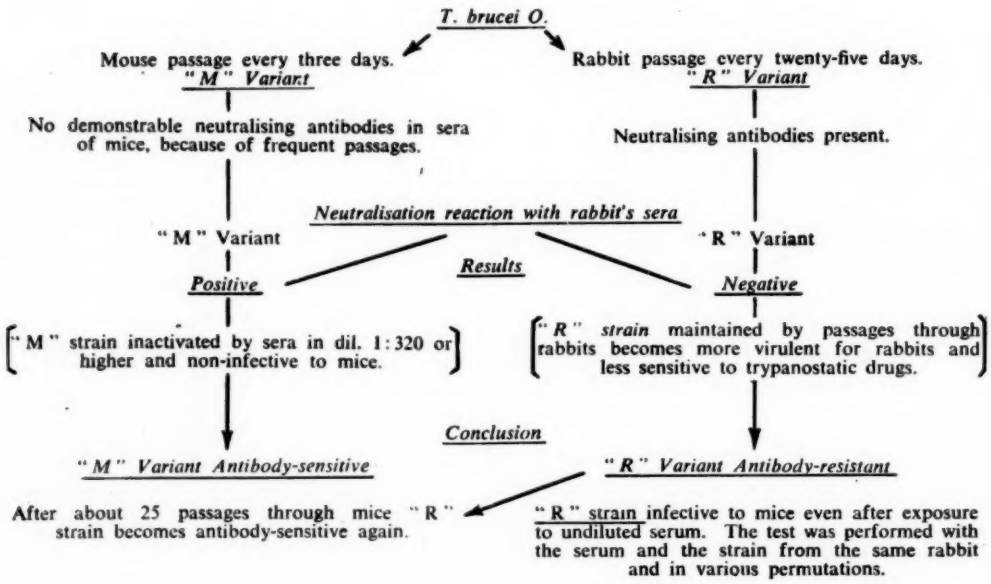
T. brucei O.
Mouse passage every three days.
"M" Variant
Rabbit passage every twenty-five days.
"R" Variant
No demonstrable neutralising antibodies in sera of mice, because of frequent passages.
Neutralising antibodies present.
Neutralisation reaction with rabbit's sera
"M" Variant
"R" Variant
Results
Positive
Negative
"M" strain inactivated by sera in dil. 1:320 or higher and non-infective to mice.
"R" strain maintained by passages through rabbits becomes more virulent for rabbits and less sensitive to trypanostatic drugs.
Conclusion
"M" Variant Antibody-sensitive
"R" Variant Antibody-resistant
After about 25 passages through mice "R" strain becomes antibody-sensitive again.
"R" strain infective to mice even after exposure to undiluted serum. The test was performed with the serum and the strain from the same rabbit and in various permutations.

TABLE II

SENSITIVITY OF *T. brucei O.* PASSAGED THROUGH TWO DIFFERENT SPECIES OF ANIMALS TO CHEMOTHERAPEUTIC DRUGS

Chemotherapeutic tests	Chemo-therapeutic drugs	*T. brucei O.* Passaged through mice. "M" variant	*T. brucei O.* Passaged through rabbits. "R" variant
Exposure of trypanosomes to drugs in vitro. The minimum amount of drugs to make trypanosomes non-infectious to mice after exposure to drugs *in vitro.*	suramin	0·004 mg./ml.	0·2 mg./ml.
	antrycide sulphate	0·004 mg./ml.	0·2 mg./ml.
Therapeutic test The minimum therapeutic dose to control the disease in mice	suramin	0·1 mg.	0·3 mg.
	antrycide sulphate	0·1 mg.	0·3 mg.
Prophylactic effect of drugs The period during which rabbits resisted infection	suramin	4 months	2 months
	antrycide pro-salt	2 months	None

Although it is possible experimentally to develop drug resistance without antibody resistance, it seems unlikely that such a procedure takes place in nature. However, studies on the sensitivity to antibodies of drug resistant strains isolated in the field may show us whether the drug resistant strains are also antibody resistant and further show us if it is true that before trypanosomes become drug resistant they have to become first antibody resistant.

These studies, of course, can only be carried out in local conditions.

Studies on Acquired Resistance to Trypanosoma congolense in Cattle

Soltys (1955) when working in Africa demonstrated that cattle treated prophylactically with antrycide pro-salt and kept in infected areas acquired a resistance to trypanosomes which persisted for a period of investigations of 18 months, and after for a further period of 2 years, without any further treatment.

These very promising results suggested the need for further field studies in another area. The second experiment, which was a repetition of the first with a slight modification, was arranged in another area infested with different tsetse flies. The second experiment was carried out with the co-operation of the Kenya Veterinary Department. Thirty cattle which had never before been exposed to trypanosomes were brought from the Kenya Highlands to the experimental area and divided into 3 equal groups, A, B and C. In addition to the experimental groups, control animals were introduced periodically to the experimental area in order to find how soon non-treated animals would become infected. *Group A* were each given antrycide pro-salt and 5 ml. of blood from an infected cow of the control animals at intervals of 2 months for a period of one year. The inoculations of infected blood were given subcutaneously on or near the date of antrycide pro-salt treatment with the idea that additional introduction of trypanosomes might increase the development of acquired immunity in this group of animals.

Group B received only antrycide pro-salt injections for the same period as group A. *Group C* were given antrycide pro-salt at two-monthly intervals on 3 occasions only.

The results of this experiment are summarised in Table III.

In group A 5 of the 10 animals survived the period of 18 months and did not show any signs of infection. Three animals became infected with *T. congolense* within 12 months and the remaining 2 animals died from extraneous causes (one died of anaplasmosis and another was killed by lions).

In group B 6 animals remained uninfected for a period of 18 months, one became infected with *T. congolense* and the 3 remaining animals died of causes other than trypanosomiasis (East Coast fever).

In group C all animals except one, which according to herdsmen, was killed by lions, survived without showing trypanosomes in the blood or by gland smear examination.

TABLE III

Group	No. of cattle	Prophylactic treatment	Period of exposure to infection without any treatment	Fate of animals
			Months	
A	10	Antrycide pro-salt 2·5 gm. at intervals of 2 months for a period of 1 year. Blood from a cow infected with *T. congolense* at intervals of 2 months	18	5 survived. 3 became infected with *T. congolense.* 2 died of various extraneous causes.
B	10	Antrycide pro-salt 2·5 gm. at intervals of 2 months. 6 injections	18	6 survived. 1 became infected with *T. congolense.* 3 died of various extraneous causes
C	10	Antrycide pro-salt 2·5 gm. at intervals of 2 months. 3 injections.	18	9 survived. 1 killed by lions.
		Controls		
D	12	No treatment. 2 animals were brought to the experimental area every 3 months.	18	All animals became infected with *T. congolense* within 4 to 8 weeks.

Animals which received antrycide pro-salt, but were not exposed to infection during prophylactic treatment, resisted infection only for a period of 2 months after the last injection of antrycide.

Control animals, which were introduced periodically into the experimental area became infected within 8 weeks.

In comparing these results (see Table III) it appears that groups B and C showed a higher percentage of non-infected animals than group A. This is not surprising, as group A received in addition to the drug, blood from infected cows. Following the promising results of these two experiments, the Kenya Veterinary Department repeated these experiments on hundreds of animals in different areas. According to the Annual Report of the Zoological Section of the Kenya Veterinary Department for 1955-56 it appears that it is possible to keep animals which receive only 3 injections of antrycide pro-salt at two-monthly intervals free from trypanosomiasis for a period of 3 years and possibly longer. This is only possible in the areas which are not heavily infested with tsetse flies. In the experiments of the Kenya Veterinary Department on 400 native cattle kept in relatively heavily infested areas 20 per cent. of animals became infected after 6 months in spite of bi-monthly antrycide pro-salt injections. It is probable that in the heavily infested areas the chances of mechanical transmission of antibody resistant strains by tsetse flies are greater than in an area lightly infested with tsetse flies. This theoretical assumption could be confirmed by further studies of the cyclical and mechanical transmission of antibody sensitive and antibody resistant strains and also by further studies on chemoprophylaxis and acquired immunity in cattle exposed to artificial infection by inoculating antibody sensitive strains and antibody resistant strains. The immunity acquired in cattle against trypanosomes after recovery from infection reported by Bevan (1936) and Van Saceghem (1938) and in cattle treated prophylactically with drugs by Soltys (1955) brings back the old problem whether it would be possible to immunise animals against trypanosomes. Various attempts have been made to prepare by various methods vaccines against trypanosomes, but in almost all cases results have been disappointing because only some proportion of vaccinated animals resisted infection and the remaining animals succumbed to infection. This failure created an idea that immunity is absolutely specific and that immunisation with one strain will not protect against infection with another strain of the same species of trypanosome. In view of recent studies by Soltys (1957) it appears that the failure of these early attempts was due rather to antibody resistant strains than to different strains, as it has been shown by the author (1955) that cattle immune to one strain of *T. congolense* were resistant to other strains obtained from various areas. This subject on immunisation of animals by using either dead or living strains is under investigation. In order to overcome the implication of antibody resistant strains, mixtures of vaccine with chemotherapeutic drugs are used and the preliminary results in rabbits are very promising. It is hoped that further field studies with a new approach carried out in local

(*Concluded at foot of adjoining column*)

conditions may throw some more light on this old problem.

The Surgical Correction of Damaged Toes in Greyhounds*

BY

J. J. DAVIES

West Ham

IN introducing this subject it is important to recall the anatomy of the dog's foot and, in particular, the nomenclature of the toes. In the greyhound world these are known by being numbered 1st, 2nd, 3rd and 4th, from inside to outer, and the joints 1st, 2nd and 3rd, from above to below.

Toe injuries incurred during racing may be either fractures of bone or injuries to joints. Fractures are not very frequent and occur mainly in the metatarsal and metacarpal bones, usually number 4. One might get more than one fractured at the same time; sometimes up to four on the same foot. Toe number 4 suffers most frequent injury.

Fractures are quite easily detected, the part swells up quickly, it is painful and crepitus can be felt. Damaged toes have to be corrected at once and any fracture set as soon as possible. With fracture of the phalanges, it is wise to have an X-ray taken at once because it does help to establish whether the joint is involved in the fracture or not. If the fracture involves a joint it means doing something more than merely correcting the displaced bones. The first thing is to examine the X-ray plate and then set the fracture. The only way to set the fracture is by putting it in plaster, this usually means putting the whole foot in plaster and taking it up to an inch or so below the tarsus or carpus. It is rather difficult to keep the plaster on more than 2 or 3 weeks, and if the animal shows signs of worry or tries to interfere it should be taken off at once. After removal of the plaster, there should be a further examination. Usually the bone will need strapping for another 2 or 3 weeks to get a good union. Normally a fractured toe takes about 2 months to heal completely. When the plaster is removed one should study the X-ray again and if the fracture is still painful then something else will need to be done—usually one finds that this means that the third joint has to be removed.

By far the most common injury to the greyhound's toe is an injury to a joint. At the track with which I am associated and during the last 3 years, 96 injuries to joints have occurred: the track is the largest in

* A Paper presented to the meeting of the Central Veterinary Society on January 2nd, 1958.

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the country, the bends are wide, and therefore toe injuries are less common than on most other tracks. The position of these 96 injuries is shown in Table I.

TABLE I

	Near fore				Off fore			
	1	2	3	4	1	2	3	4
1	3	1	—	16	—	—	—	1
2	7	6	1	16	—	4	4	3
3	4	—	—	—	2	—	—	2
	Near hind				Off hind			
1	3	—	1	8	1	1	—	4
2	—	1	—	—	1	1	5	—
3	—	—	—	—	—	—	—	—

Total 96 ; Near fore 54.

From this survey it can be seen that the near fore suffers the most; 54 injuries involving this limb are recorded, more than half of the total number. The number 4 toe on the near fore limb suffered a third of the total injuries. The reason for this is that the near fore is the most vulnerable, it is the leg which takes most of the strain as the dog goes round the track in an anti-clockwise direction.

The actual injury to the joint consists of a tearing of the lateral ligament, usually it is the internal lateral ligament. There is a tendency in going round the track for the body to swing outwards and therefore the internal ligament takes most of the strain. The injuries to the joint may vary from a simple strain to a complete dislocation. Sometimes the two middle toes at the middle joints may be completely dislocated but it is always the internal lateral ligament which suffers.

With greyhounds the main object of treatment is to get the dogs back into racing as quickly as possible and with toe injuries one expects to get them back fairly quickly. Provided treatment is available " on the track" one can deal with the injury straight away and it is then much simpler to correct the lesion. If it is a simple strain, treatment merely requires that the foot be bandaged firmly for a week or two and the dog can then be returned to racing in about 3 weeks. If there is considerable injury to the joint, it is best to immobilise it straight away and put it in plaster for a week or so before deciding on further treatment. The degree of injury can be decided by the movement in the joint. When examining injuries of the first joint it is best to try to rotate the joint and if there is considerable movement it means taking the end joint off. With the middle or 2nd joint it is a question of determining the degree of side-to-side movement whereas, with the terminal joint, first try to dislocate it to decide whether it has to be removed or corrected before the dog can race again. If it is decided to plaster the injury one has to decide when the plaster is removed whether something further must be done. The ideal to be aimed at is to get the dog back racing without mutilating the foot. There is a limit to what can be done, one can not remove more than the third joint; if more is removed the foot is spoilt. The aim should be to do as little mutilating as possible and in fact the majority of injuries to joints can be corrected by shortening the nail. One can also risk firing the joint as it seems to help in repairing joints.

The other alternative is to remove the third joint. The operation for shortening the nail is simple. Local anaesthesia is induced by procaine with adrenalin. The nail is then clipped as short as possible and the injured joint fired. For firing, 6 holes are punctured round the joint, one on each side and one in the middle, above and below. The foot is then bandaged and the nail heals in about 3 weeks. The dog is then fit to race in a month or 6 weeks from the date of operation. The purpose of shortening the nail is partially to put the toe out of action.

The operation of removing the toe is done by anaesthetising the toe in the same way, and by filleting the toe from the nail to above the third joint, puncturing the joint and removing the third phalanx as well as the epiphysis of the second phalanx.

It is wise to have the pad drawn well up to the second phalanx and the operation is finished off with one deep suture on each side and two smaller sutures to close the gap. The foot should be bandaged and the sutures removed after a week or so. The dog will be fit to race in 4 to 6 weeks.

There are two other injuries that should be mentioned. The first concerns the dewclaw. Greyhound owners insist on leaving the dewclaw on and maintain that it does assist the dog to negotiate bends. Frequently the nail is cracked or shelled. the distal joint may be dislocated or the 2nd phalanx fractured. If these injuries are severe it is best to remove the whole dewclaw.

The other injury concerns the No. 3 or distal joint of a No. 1 toe. The nature of this is a dislocation with splitting of the skin over the inner aspect of the joint, resulting in a true open joint. This will heal and scar over but will invariably recur when the dog is raced. The only treatment is to remove the joint.

100th ANNIVERSARY OF THE FOUNDATION OF THE ROYAL VETERINARY AND AGRICULTURAL COLLEGE OF DENMARK

The centenary celebrations will be held in the presence of the King and Queen of Denmark on Thursday and Friday, September 4th and 5th, 1958, and besides the actual ceremony will include a gala performance in the Royal Theatre and a banquet given by the Minister of Agriculture.

The President of the R.C.V.S., Professor T. J. Bosworth, has, through the Foreign Office, received an official invitation to partake in these ceremonies, which he has accepted on behalf of the veterinary profession of the United Kingdom.

The Excretion of Steroids by Animals

BY

A. A. WRIGHT

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SUMMARY.—1. *The excretion of steroids by the mare, cow, and goat is described. Considerable species differences are shown.*

2. *The importance of faecal excretion in the cow is suggested.*

3. *Some methods of steroid estimation are discussed in relation to the known constituents of animal urines.*

THE investigation of urinary metabolites plays an important part in the study of hormone balance in the human being (Loraine, 1958). Methods for the determination of steroids are continually being worked out and the best of these are specific for individual steroids. Recent examples are the pregnanediol method of Klopper, Michie, and Brown (1955) and the oestrogen determinations of Bauld (1956) and Brown (1955). The last-mentioned has recently been modified to increase its specificity by Brown, Bulbrook, and Greenwood (1957). Before any estimation of this sort can be made it is obviously necessary to identify the metabolites which are present. Whereas the steroids of human urine have been frequently investigated, comparatively little has been done to identify those present in animal urines. Such work has shown that different species have quite different excretory patterns and it is this aspect which will be emphasised. Most of the values given for concentrations should be taken as very approximate.

Oestrogens

Although some species do excrete small amounts of oestradiol-17β†, this hormone is usually metabolised to give compounds of lower biological activity. The excretory patterns of 4 species are shown in Table I. The metabolites of human pregnancy urine have been included for comparison. The major product is oestriol.

Klyne and Wright (1957) found that the chief C_{18} steroid of pregnant goat's urine was oestrone (0.3 mg. per l.); a smaller quantity of oestradiol-17α* (0.1 mg. per l.) was also present. These compounds were also present in similar concentrations in pregnant cow's urine (Klyne & Wright, 1956). These authors used the Kober reaction to measure total oestradiol and an acetic-sulphuric acid reagent to measure oestradiol-17α (I). Using these two methods on all fractions which might contain oestradiol, little or no oestradiol-17β could be detected in pregnant goat's urine. A thorough investigation of the numerous fractions from cow's urine was not made, but no evidence for the presence of oestradiol-17β was obtained. Oestriol was not found either in the goat or in the cow. Pope, McNaughton, and Jones (1957) also found oestrone as the main oestrogen metabolite of pregnant cow's urine. El-Attar and Turner (1957) and Velle (1958), using milder methods of hydrolysis found larger quantities of oestradiol than of oestrone.

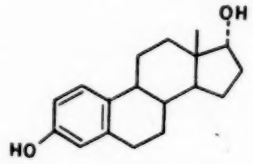

FIG. 1.—Oestradiol-17α.

Woods (1950) reported the presence of oestrone, oestradiol and an "oestriol-like" compound in the urine of cows in the 13th to 18th week of pregnancy. The third compound was shown not to be oestriol, although it behaved like it in some ways. It is possible that this is a non-steroid compound like the equol found by Suemitsu and his colleagues (Suemitsu & Huira, 1953; Suemitsu, Huira & Nakajima, 1955) and also by Klyne and Wright (1956) in cow's urine. Marker (1939a) has isolated oestrone from bull's urine (40 μg. per l.).

* The work of the author, cited in this paper, was carried out at the Postgraduate Medical School of London during the tenure of an Agricultural Research Council grant

† Formerly called "α"-oestradiol.

* Formerly called "β"-oestradiol.

TABLE I

URINARY EXCRETION OF OESTROGENS DURING PREGNANCY

	Oestrone	Oestradiol-17β	Oestradiol-17α	Oestriol	Equilin	Equilenin
Cow	+		+			
Goat	+		+			
Mare*	+	+	+		+	+
Human*	+	+		+		

*The mare also excretes 17-dihydroequilin and 17-dihydroequilenin. 16-*epi*Oestriol and 16-hydroxyoestrone are also found in human urine (Marrian & Bauld, 1955; Watson & Marrian, 1956; Marrian, Loke, Watson & Panattoni, 1957). Other references in text.

Oestrone is also the main phenolic steroid excreted by the mare up to mid-pregnancy (up to 200 mg. per l.; Beall and Grant of Ayerst McKenna, Montreal, personal communication). In late pregnancy the *B*-ring unsaturated ketones (equilin and equilenin) predominate. Non-ketonic oestrogens are also found and these are mainly 17α-compounds (Hirschmann & Wintersteiner, 1938). Oestradiol-17α is predominant among these up to mid-pregnancy, but this is increasingly replaced in the later stages by the 17-dihydro derivatives of equilin and equilenin (Beall & Grant; Glen, Barber, McConkey & Grant, 1956). Earlier workers (Wintersteiner, Schwenk & Whitman, 1935; van Stolk & de Lenchère, 1937) isolated oestradiol-17β from pregnant mare's urine. It does not appear to have been found since and Wintersteiner (1937) commented on this, suggesting that differences in the method of extraction may account for it. Further work is required to settle this point since it is possible that other explanations, such as a difference in the physiological state of the animal, may account for the discrepancy. It is interesting that stallion's urine contains an even higher concentration of oestrogen than mare's urine (Zondek, 1934; Jensen, Larivière & Elie, 1945; Levin, 1945b).

Other points of interest arise. The change at mid-pregnancy in the nature of the excreted products is interesting and requires explanation. The total amount of oestrogen excreted also tends to fall after mid-pregnancy in the mare (Kober, 1938) which is in contrast to the excretion by the pregnant cow. In the latter animal the excretion of urinary oestrogens rises exponentially throughout pregnancy (Turner, Frank, Lomas & Nibler, 1930). Furthermore, the recent work of Heard and his collaborators, using radioactive precursors (Heard, Bligh, Cann, Jellinck, O'Donnell, Rao & Webb, 1956), suggests that the unsaturated oestrogens, equilin, equilenin, and their 17-dihydro derivatives, are not derived from oestrone or oestradiol but are synthesised by a somewhat different route.

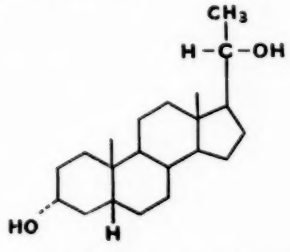

FIG. 2.—5β-Pregnane-3α:20α-diol.

Neutral Steroids: Non-Ketonic Alcohols

C_{21} Diols. 5β-Pregnane-3α:20α-diol (II) has been recognised as the major metabolic product of progesterone in man and in the rabbit (Heard, Bauld & Hoffmann, 1941). It is quantitatively the most important neutral steroid in human pregnancy urine (about 50 mg. per l. in late pregnancy). Traces of other diols have been found. It is not found in all species; in the mare steroids of the 5α (*allo*pregnane) series predominate. The excretion of C_{21} diols by 4 species is shown in Table II.

5β-Pregnane-3α:20α-diol is the major neutral steroid of pregnant goat's urine (Klyne & Wright, 1957) but the concentration is only 2 mg. per l. It was thought that this compound was absent from cow's urine but some evidence has been obtained to suggest that it is present in very small quantities (Klyne & Wright, unpublished). Claims for the isolation of this compound from the urine of bulls (Marker, Wittle & Lawson, 1938) and pregnant cows (Marker, 1938), in concentrations of 26 mg. per l. and 7 mg. per l. respectively, have been made. Two other diols were also obtained (see Table II), but none were found in steer's urine (Marker, 1939b). It is difficult to reconcile these conflicting reports, but the work of Strickler, Walton, and Wilson (1941), Stevenson (1947), and Hill, Peterson, and Cohen (1954) supports the conclusions of Klyne and Wright. The isolation of C_{21} diols from cattle bile (Pearlman, 1946; Pearlman & Cerceo, 1948; Antia, Mazur, Wilson & Spring, 1954) suggests that the results of Marker may have been due to gross faecal contamination of the urine. 5β-Pregnane-3α:20α-diol has also been isolated from pregnant sheep's urine (Coulson & Robertson, private communication).

The diol fraction of pregnant mare's urine is a complex mixture. Marker and his collaborators claimed to have isolated 5β-pregnane-3α:20α-diol and the two epimeric 5α-pregnane-3:20α-diols, 5α-pregnane-3β:20α-diol being quantitatively the most important (Marker & Rohrmann, 1939a). The isolation of pregn-5-ene-3β:20α-diol (Marker & Rohrmann, 1938) and uranediol (Marker, Rohrmann & Wittle, 1938) were also reported. Other workers have not confirmed all these results. Bauld and Heard (1940) isolated 5α-pregnane-3β:20β-diol (III). This compound, together with its 20α-epimer and uranediol (a C_{21} diol shown by Klyne and Shoppee (1952) to be a *D*-homo steroid, with a six-membered *D*-ring, IV) were the main components of the mixture of diols isolated from pregnant mare's urine by Brooks, Klyne, Miller and Paterson (1952). The relative proportions of these three compounds

TABLE II

URINARY EXCRETION OF C_{21} DIOLS DURING PREGNANCY

	5β-Pregnane-3α : 20α-diol	Pregn-5-ene-3β : 20α-diol	5α-Pregnane			"Uranediol"
			-3α : 20α-diol	-3β : 20α-diol	-3β : 20β-diol	
Cow	+		+	+		
Goat	+					
Mare	+	+	+	+	+	+
Human	+		+	+		+

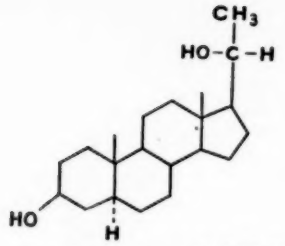

FIG. 3.—5α-Pregnane-3β : 20β-diol.

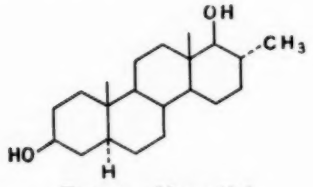

FIG. 4.—Uranediol.

apparently vary with the state of pregnancy (Klyne, unpublished), uranediol and the 20β compound predominating in late pregnancy. The mare thus shows a change in the nature of the presumed progesterone metabolites as well as oestrogen metabolites as pregnancy progresses.

C_{19} Diols. The major neutral steroid of pregnant cow's urine was shown to be 5β-androstane-3α : 17α-diol (Wright & Klyne, 1957), though its concentration in the urine was only 0.2 mg. per l. The isolation of this substance from the urine was not unexpected since it had been found in pregnant cow's bile by Pearlman and Cerceo (1948). 5β-Androstane-3α : 17α-diol (V) was also obtained from the pregnant goat's urine in similar amounts.

The presence of this C_{19} compound is interesting especially as it has the 17α configuration. Evidence was also obtained for the presence of 5α-androstane-3β : 17α-diol in small amounts. Paper chromatography indicated that others might also be present.

Compounds of this type have not been isolated from urine very frequently. The pregnant mare excretes two 5α-androstane-3 : 16-diols (Brooks & Klyne, 1957) which are interesting since they have no 17-substituent. 5β-Androstane-3α : 17β-diol and androst-5-ene-3β : 17β-diol have been isolated from human urine. The presence of 17β-isomers in pregnant cow and goat urine is not excluded since these compounds were found to be difficult to detect, but it does not seem likely that they would be present in any significant quantity (Klyne & Wright, unpublished). The occurrence of C_{19} diols in urine is illustrated in Table III.

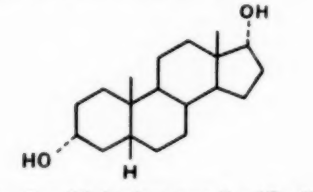

FIG. 5.—5β-Androstane-3α : 17α-diol.

Ketosteroids

Little work has been reported on the isolation of 20-ketosteroids from animal urine. None has been obtained from the urine of cows or goats. Both 5α- and 5β-pregnane-3 : 20-diones and uranolone have been isolated from mare's urine (Marker, Lawson, Wittle & Crooks, 1938), also 3β-hydroxy-5α-pregnan-20-one (Heard & McKay, 1939). Klyne, Schachter, and Marrian (1948) isolated 3β-hydroxy-5α-pregn-16-en-20-one which may be related to the 5α-pregnan-3β : 16α : 20β-triol so typical of mare's urine. 3α-hydroxy-5β-pregnan-20-one and 3β-hydroxy-5α-pregnan-20-one have been isolated from sow's urine (Marker & Rohrmann, 1939b).

17-Ketosteroids. Many workers have carried out 17-ketosteroid determinations on animal urines but few isolations have been reported. Klyne & Wright (1957) isolated one 17-ketosteroid, *epi*androsterone (3β-hydroxy-5α-androstan-17-one), in an impure condition from pregnant goat's urine. The amount isolated represented a concentration of less than 0.1 mg. per l. in the urine. Paper chromatography and infra-red spectra indicated the presence of androsterone (3α-hydroxy-5α-androstan-17-one), aetiocholanolone (3α-hydroxy-5β-androstan-17-one), and 11-oxoaetiocholanolone (3α-hydroxy-5β-androstane-11 : 17-dione) in the α fraction. Holtz (1957) obtained evidence for the presence of androsterone, aetiocholanolone, and 11-oxoaetiocholanolone in the urine of normal and ACTH-stimulated cattle. Dehydro*epi*androsterone (3β-hydroxyandrost-5-en-17-one) was also present. He estimated that the total excretion of 17-ketosteroids was probably not more than 0.3 mg. per l. The work of Klyne and Wright (unpublished) on pregnant cow's urine is in general agreement with these results. Marker (1939a, b) reported the isolation of androsterone and dehydro*epi*androsterone from the urine of bulls, cows, and steers in very low yields (7 to 40 μg. per l.). These low figures are supported by the results

TABLE III

URINARY EXCRETION OF C_{19} DIOLS

	5β-Androstane		Androst-5-ene	5α-Androstane		
	-3α : 17α-diol	-3α : 17β-diol	-3β : 17β-diol	-3β : 17α-diol	-3β : 16α-diol	-3β : 16β-diol
Cow	+			+		
Goat	+			+		
Mare					+	+
Human		+	+			

TABLE IV

URINARY EXCRETION OF 17-KETOSTEROIDS

	3α-hydroxy-5β-androst-an-17-one	3β-hydroxy-androst-5-en-17-one	3α-hydroxy-5α-androst-an-17-one	3β-hydroxy-5α-androst-an-17-one	3α-hydroxy-5β-androst-an-11 : 17-dione
Goat	+		+	+	+
Cow	+	+	+		+
Mare		+		+	
Human	+	+	+	+	+

of bioassay of urinary androgens in cattle (Koch, 1937; Butz & Hall, 1938; Wiseman & Schultze, 1953).

Among the species so far investigated, appreciable quantities of ketosteroids have been found only in the urine of human beings and guinea-pigs (Peron & Dorfman, 1956). Oppenauer (1941) was able to identify dehydro*epi*androsterone and *epi*androsterone from pregnant mare's urine but the yields were low. Many compounds have, however, been isolated from human urine in addition to those shown in Table IV which summarises the reports on 17-ketosteroids in animal urines.

Excretion of Steroids via the Gut

With the use in recent years of steroids containing radio-isotopes the importance of faecal excretion of steroid metabolites has been increasingly recognised. This route may be the most important one in some species. Bradlow, Dobriner, and Gallagher (1954) found that in mice 31 per cent. of the radioactivity of cortisone injected intravenously was found in the faeces; 65 per cent. was in the faeces when intramuscular injection was used. Rats excrete, in the faeces, more than half the radioactivity of administered testosterone (Ashmore, Elliott, Doisy & Doisy, 1953), progesterone (Shen, Elliott, Doisy & Doisy, 1954), and corticoids (Hyde & Williams, 1954; Bocklage, Doisy, Elliott & Doisy, 1955; Wyngaarden, Peterson & Wolff, 1955).

The presence of androgens in the faeces of pregnant cows was first demonstrated by Riley and Hammond (1942). Since then Turner and his coworkers, in a long series of papers (Turner, 1947a, b, 1948, 1949; Miller & Turner, 1951, 1953, 1955) have investigated the properties and occurrence of this androgen. The amount present was raised on the administration of progesterone (Miller & Turner, 1955), and by injecting 5 g. of progesterone into cows over five days, Miller, Turner, Fukushima, and Salamon (1956) were able to isolate some of the compounds formed. These were 5α- and 5β-androstane-3:17-dione, androst-4-ene-3:17-dione, and androsta-1:4-diene-3:17-dione. Gassner and Longwell (1947) and Longwell and Gassner (1947), have also investigated this problem but they appear to consider that the androgens may arise from the adrenals. Levin (1945a) showed that an oestrogen, probably oestradiol, was present in cow faeces.

The isolation of steroids from bile has shown the route whereby these compounds may enter the gut. Cantarow and his associates, working with dogs, have emphasised the importance of biliary excretion (see for example Paschkis, Cantarow, Rakoff, Hansen & Walkling, 1944). Pearlman (1949) discussed the subject when considering the rôle of the liver in steroid metabolism. Pearlman (1946), Pearlman, Rakoff, Cantarow, and Paschkis (1947), and Pearlman and Cerceo (1948) isolated the following compounds from the gall-bladder bile of pregnant cows: oestrone, 5α-pregnane-3β:20β-diol, 5β-pregnane-3α:20β-diol, 5β-androstane-3α:17α-diol (referred to by Pearlman and Cerceo as aetiocholane-3α:17β-diol), 3β-hydroxy-5α-pregnan-20-one, and an unknown. The presence of 5β-pregnane-3α:20β-diol was confirmed by Antia, Mazur, Wilson, and Spring (1954). Glick (1957) also isolated small quantities of two corticoid derivatives, tetrahydrocortisol and tetrahydrocortisone, from cow bile. It is interesting that a species of *Fusarium* can convert progesterone and related compounds to androsta-1:4-diene-3:17-dione (Vischer & Wettstein, 1953). Species of this genus may occur in the rumen. Casady, Cole, and Hart (1949) observed that the quantity of androgen in the faeces was influenced by the diet of the animal. As the diet affects the intestinal flora this further supports the suggestion of Dorfman (1957) that the androgens of cow faeces arise by microbial transformation in the gut. While it is possible for the steroids to be reabsorbed from the gut, their presence in the faeces shows that the reabsorption is, at least, incomplete. Since steroids that do not appear in the urine are found in the bile, it is possible that this represents a major excretory pathway in the cow. Positive evidence for this view has recently been obtained by El-Attar and Turner (1957) who determined, by a chemical method, the oestrogens in the faeces and urine of cows.

Methods of Estimation

Of the methods used for the estimation of urinary steroid metabolites, only the Kober reaction was worked out for use on the urine of domestic animals. This reaction appears to be fairly specific for oestrogen metabolites, but is not suitable for use with the urines of cows owing to the large amounts of phenolic compounds excreted, whilst the quantities of oestrogen are small. Other methods for human urine, including those designed to estimate individual steroids, do not appear to be generally applicable to animal urines.

Oestrogen Determinations. The Kober reaction may be used on mare's urine extracts to gain an over-all picture of oestrogen excretion (Kober, 1938). The determination of the individual oestrogen metabolites in this species is complicated by the number

of compounds which may be present. No method has been proposed for this, although certain constituents, *e.g.* equilenin, may be estimated by specific reagents (see Grant & Beall, 1950). The metabolites of cow's urine, oestrone, and oestradiol, may perhaps be estimated by some modification of the methods of Brown (1955) or Bauld (1956). The behaviour, in these methods, of other constituents of the phenol fraction, *e.g.* equol, has not been thoroughly investigated though equol itself does not interfere seriously in the final colour reaction (see Klyne & Wright, 1957). The presence of oestradiol-17α rather than the 17β isomer of human urine adds a further complication.

Pregnanediol Determinations. All the methods for determining pregnanediol have been worked out for use on human urine. These can be of no use in their present form for work on the cow, which excretes only negligible amounts, or on the mare which excretes different isomers. They could probably be used on pregnant goat's urine but here interference would be found from substances with similar properties. For example, the method of Klopper, Michie, and Brown (1955) would estimate unknown and possibly variable amounts of 5β-androstane-3α: 17α-diol and some unknown compounds (Klyne & Wright, unpublished).

17-Ketosteroid Determinations. The estimation of 17-ketosteroids has been used in endocrinological studies on animals but the values recorded do not appear to be related to the steroid content of the urine. Cattle urines give values of 20 to 40 mg. "apparent ketosteroid" per l., although only about 0.3 mg. per l. of true ketosteroids are present. This has been fully discussed by Holtz (1957), who was able to attribute most of the colour to ionone compounds. Similarly Klyne and Wright (1957) recorded values of 7 to 10 mg. per l. of "apparent ketosteroids" in pregnant goat's urine although less than 1 mg. per l. was subsequently found by fractionation. Conclusions drawn from the results of 17-ketosteroid determinations on animal urines are therefore of doubtful value.

Corticoid Determinations. No evidence is available for assessing the usefulness of corticoid determinations. Holcombe (1957) has given evidence for the use of a determination of "reducing corticoids." The values obtained by this method would suggest that far more corticoids are excreted than any other steroid in these urines. It remains to be tested whether this technique is susceptible to interference by any other compounds. It is at least suggestive that the Porter-Silber reaction, which appears to be specific for the dihydroxyacetone structure, gives very low values with cattle urines (Holm & Firch, 1955).

Conclusions

The following conclusions, which have been stated previously, may be drawn from this study of the steroids of animal urines.

1. Methods designed for the estimation of specific compounds are not of universal applicability owing to the different nature of the steroids excreted by different animals.

2. A thorough qualitative investigation of steroid metabolites should be made before their estimation is undertaken.

3 Care must be undertaken in applying to animal urines, which may contain unknown, interfering substances, methods designed for human urine.

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Cardiac Arrest and Its Treatment

BY

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SUMMARY.—1. *The causes of cardiac arrest are briefly mentioned.*

2. *The history and technique of cardiac massage is outlined.*

3. *The history of the successful treatment of cardiac arrest in a cat is given.*

"CARDIAC arrest is an emergency which may face any surgeon, at any time." These are the opening words of the Hunterian Lecture delivered by B. B. Milstein at the Royal College of Surgeons in 1956, and apply equally to veterinary and human surgeons. If successful measures are to be taken to overcome this catastrophe they must be immediate and unhesitating for the brain can only withstand anoxia for a period of 3 to 5 minutes, and the possibility of pre-existing anoxia before actual cardiac arrest gives an even smaller margin of time. If the restoration of cardiac function is delayed beyond this safety margin, the resultant cerebral anoxia will give rise to most serious neurological sequelae and even decerebration.

Although John Hunter demonstrated the possibility of overcoming cardiac arrest in tracheotomised animals by instituting artificial respiration, the first man to try direct cardiac massage was Moritz Schiff who, in 1874, published his investigations of the cause of death in dogs due to the administration of chloroform and ether. He was unable to repeat John Hunter's experiments, but advocated the technique of "rhythmic movements of the hand holding the whole heart" to restore cardiac action. He pointed out that it was not mechanical stimulation of the myocardium that produced the effect, but the re-establishment of coronary blood flow by means of the cardiac compression.

The first report of successful cardiac massage in man was by Starling and Lane in 1902, who performed cardiac compression through the intact diaphragm, although in 1901 successful cardiac massage was performed by direct approach through a thoracotomy incision, but was not reported until 1904 (Igelsrud, 1901).

Milstein (1956) classifies cardiac arrest as either ventricular fibrillation or cardiac asystole. Milstein and Brock (1954) published their observations on a series of 30 patients who developed ventricular fibrillation during the course of cardiac operations, of whom 9 recovered. Fibrillation commonly occurs as a result of direct myocardial stimulation, or when stimulation is combined with anoxia. Cardiac asystole is generally the result of pure myocardial anoxia, or of vagal reflexes in the presence of anoxia, and is the condition most likely to be encountered in general surgery.

Anoxia may arise from an impaired airway, from inadequate pulmonary ventilation during controlled respiration, from inadequate respiratory exchange associated with the use of drugs that seriously depress the respiratory centre, and from the administration of an anaesthetic mixture containing too low a concentration of oxygen.

Cardiac arrest is commonly precipitated by acute respiratory obstruction due to the inhalation of vomitus or rumenal contents. It is also precipitated by a massive arterial haemorrhage, or by a continued slow blood loss without adequate replacement which, combined with operative trauma, will result in a fall in blood pressure to a level at which coronary flow is unable to be maintained.

Recognition and Treatment

The recognition of cardiac arrest has been the subject of considerable controversy, but undoubtedly the most reliable sign is the absence of a peripheral pulse (Gerbode, 1955). In the veterinary patient in which the peripheral pulse is sometimes difficult to detect, one can add cessation of voluntary respiration, pupillary dilatation and cyanosis, with no detectable heart beat on auscultation.

At this stage, treatment must be immediate, and aimed at the initiation of artificial respiration, preferably with pure oxygen, together with cardiac massage. Beck (1955) emphasises the need for extreme speed in opening the chest and starting cardiac massage, pointing out that even stopping to sterilise the skin prior to thoracotomy is wasting precious seconds, and must be dispensed with.

Adequate oxygenation and control of respiration can only be attained by endotracheal intubation and manual compression of the rebreathing bag, which serves the double purpose of oxygenating the blood and improving pulmonary circulation.

Cardiac massage is best performed through a thoracotomy incision (Milstein & Brock, 1954; Milstein, 1956; Gerbode, 1955; Beck, 1955). Although successful resuscitation has been carried out through trans-diaphragmatic massage from the abdomen, the main objections to this are the fact that the heart is not under direct vision, and that the approach makes the application of defibrillating electrodes difficult in cases of ventricular fibrillation.

Care must be taken while handling the myocardium during massage. Adelson (1957) published autopsy findings on 60 patients who died during or following cardiac massage. Myocardial damage varied from multiple subepicardial petechiae or zones of haemorrhagic extravasation, to gross laceration of the heart. He pointed out that the cardiac injuries produced were a function of the technique used rather than the duration of massage. Haight and Sloan (1955) record perforation of the heart. Milstein states that the palmar surfaces of the fingers, and not just the tips, should be used for compression.

The normal rate of cardiac compression in man is approximately 50 times a minute (Milstein, 1956).

In animals it would be a reasonable criterion to approximate cardiac compression to slightly below the normal pulse rate. Whilst massage may be carried out through the intact pericardium, it is often opened to allow direct inspection of the myocardium. Venous return to the heart may be increased by the use of a head-down tilt which has the additional advantage of increasing both coronary and cerebral circulation. Massage should be continued until the whole myocardium is pink, well oxygenated, and has regained its tone, and the heart should be kept under direct observation for at least 5 minutes before attempts are made at chest closure.

In cases where cardiac massage fails to restore normal rhythm, Kay and Blalock (1951) found that injections of 1/1,000 adrenaline into the cavity of the left ventricle were effective in restoring the heart in asystole, and could be repeated in 5 minutes, but when used in excessive amounts would cause fibrillation. Where the heart does not respond to adrenaline, these writers report success in 3 cases by using calcium chloride, and suggest a dose not exceeding 5 ml. of a 10 per cent. solution for children. As with adrenaline, an overdose may produce fibrillation.

Cardiac Massage in a Cat

In this hospital, 2 cases have offered the opportunity to resort to cardiac massage. Both subjects were young cats undergoing normal flank ovariohysterectomy. Although normal cardiac rhythm was restored to the first case, the delay in instituting massage was too great, and resulted in decerebration due to cerebral anoxia. The animal survived 4 days in decerebrate rigidity, and was destroyed on humane grounds. The second case made a complete recovery.

As the anaesthetic and surgical details were the same for both cases, it is proposed to give the history of the second case as typical. Premedication was by 1/200th grain atropine sulphate, and 10 mg. pethidine hydrochloride. General anaesthesia was induced by the intravenous injection of 2½ per cent. thiopentone sodium, and maintained by a 3:1 mixture of nitrous oxide and oxygen, passing over ether, and delivered at a flow rate of 4 litres a minute from a standard Boyle anaesthetic machine *via* a Magill attachment and face mask.

The animal was positioned in right lateral recumbency, and at this stage respiration was irregular even under minimal ether. Respiratory failure coincided with the opening of the peritoneum of the left flank. The pupils were widely dilated, the mucous membranes cyanotic, and no heart sounds could be auscultated. The animal was immediately intubated with a Magill No. 2 endotracheal tube, and artificial respiration commenced with pure oxygen, by means of an Ayre's T-piece.

Without delaying to clip or sterilise the skin, thoracotomy was performed through the 6th intercostal space, and cardiac massage started through the intact pericardium. After about 25 seconds, normal heart action commenced, and almost immediately the mucous membranes assumed a normal colour. Voluntary respiratory movements started 2 minutes later, but were abolished by an intravenous injection of 4 mg. succinylcholine chloride, and from then onwards, respiration was controlled, with ether gradually being introduced into the oxygen circuit.

After observing normal heart action for nearly 7 minutes, the hair contaminating the thoracic cavity was removed, 200,000 units of sodium penicillin powder dusted into the thoracic cavity, and normal thoracotomy closure carried out, the residual pneumothorax being dispersed by momentary hyperinflation of the lungs just before the last stitch was tied. The skin was then clipped along its edges, and coapted with nylon mattress eversion sutures. Ovaro-hysterectomy was rapidly completed, and by this time voluntary respiration was re-established, and the endotracheal tube removed.

A check X-ray was taken to ensure the complete dispersion of the pneumothorax, and recovery from anaesthesia was delayed to just over 3 hours. As the cat appeared to be suffering discomfort from the thoracotomy wound, she was given 20 mg. pethidine hydrochloride.

For 24 hours the animal appeared blind, but was able to stand and walk, and defaecation and urination were normal. The pulse was maintained at 160 and respiration at 48. Normal vision returned in 24 hours, and from then recovery was uneventful. 200,000 units of sodium penicillin were given daily for 5 days, and in spite of the absence of clipping and skin sterilisation, the thoracotomy incision healed by first intention, and the animal was discharged on the 10th post-operative day.

Conclusion

Now that veterinary surgery is making such rapid advances in anaesthesia, supportive therapy, and surgical technique, it is incumbent upon all who practice surgery to be familiar with resuscitation. In the words of Claud S. Beck, "I do not think we are doing the right thing for our patients unless we have knowledge of resuscitative measures. There is no excuse, it seems to me, for a surgeon not knowing how to resuscitate a heart."

The essence of success is speed. This can only be achieved if every member of the surgical team is familiar with the procedure of cardiac resuscitation, and is prepared to carry it out without hesitation, immediately arrest is detected.

Acknowledgments.—Our thanks to Miss Valerie Langley for her patience and nursing skill, and M. C. G. Littlewort for his helpful criticism.

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Current Literature

ABSTRACTS

A Conjunctivitis Occurring in Chickens, Presumably of an Infectious Nature. VELLING, G. (1957). *Nord. Vet. Med.* **9.** 505-20.

The author records a series of 9 outbreaks of conjunctivitis occurring in Denmark in intensively reared chicks, 2 to 12 weeks old. Panophthalmia was an occasional sequel. Mortality tended to increase in successive batches of chicks, sometimes reaching 35 per cent. The disease spread to healthy chicks placed in the same cage or in the same room. The cause was not demonstrated but was believed to be a virus, with overcrowding and poor hygiene as predisposing factors.

This abstract is based on one in the *Veterinary Bulletin*, **28.** 1,790.

Relative Merits of Pellets and Mash for Laying Birds. MORRIS, T. R., & JENNINGS, R. C. (1958). *The Agricultural Review.* **3.** No. 11. 25-30.

Generally there is no significant difference between the egg production of birds receiving dry mash *ad lib.* and that of birds receiving the same ration, *ad. lib.*, in the form of pellets. It is possible, however, that some small-type hybrids may require either pellets or a high-energy mash to enable them to reach the high rates of lay of which they are capable.

Birds receiving pellets tend to put on more weight than birds receiving the same amount of mash. They may also show a higher egg yield when the food intake is limited. These differences are thought to to be due to the effect of the heat and pressure developed in the pelleting machine. This may increase the availability of some nutrient factor or, less probably, destroy some inhibitory factor.

Pellets are less wasteful than dry mash for outdoor feeding. They fail to reduce waste in batteries, but should be used in batteries of the cafeteria type if the feeding time available to each bird is less than 6 hours per day. E. A. G.

The Feeding of Cod-liver Oil to Growing-fattening Pigs. WORDEN, A. N. (1958). *J. Agric. Sci.* **50.** No. 3. 345.

Some good-quality cod-liver oil was fed to bacon pigs from weaning to slaughter age. The oil contained an antioxidant, and was fed at the rate of zero to 5 per cent. in the ration to 4 groups of cross-bred pigs. The cod-liver oil did not produce any discoloration of body fat, fishiness, or other taint, or any adverse effect upon the carcase quality as judged by routine grading measurements. All were graded "A." The final tests were made after slaughter at a bacon factory. Improvement in food conversion accompanied increases in the amount of cod-liver oil fed.

[*Abstractor's note.*—In view of the fact that fishiness or such taint is often not capable of being detected until the bacon appears on the breakfast plate, it is a pity the experiment was not carried on to that stage about a fortnight or so after the pigs were slaughtered.]

D. J. A.

The Excretion of Steroids by Animals—*Concluded.*

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News and Comment

KENNEL CLUB RULING ON ENTIRE DOGS

We are asked to remind readers of the new Show Regulations of the Kennel Club which come into force on January 1st next. These Regulations have been drawn up after full discussion with the B.V.A., and provide that, after the date mentioned above, veterinary surgeons or veterinary practitioners acting professionally at shows shall reject any dogs which are not entire, *i.e.* which have not both testicles descended and in the scrotum. Dogs which have been treated for cryptorchidism or monorchidism on veterinary advice are, similarly, not eligible to be shown and must be rejected by veterinary examiners.

The purpose of the new Show Regulations, which have the full support of the B.V.A., is to prevent the exhibition of dogs which are not entire with the intention that the use of such dogs at stud will decrease.

It has been asked whether, in the changed circumstances, it will be ethical for veterinary surgeons or veterinary practitioners to perform operations upon dogs for the correction of monorchidism or cryptorchidism. The R.C.V.S. has ruled that it is perfectly proper to perform such operations subject, of course, to the rider that the veterinarian must not be party to any scheme intended to deceive.

SUCCESSFUL PROSECUTION FOR UNQUALIFIED PRACTICE

On July 29th Mr. Joseph Fisher appeared before the Hanley stipendiary magistrate on two charges brought by the R.C.V.S. under Section 6 of the Veterinary Surgeons Act, 1948. Fisher, who was stated to be unemployed and living on national assistance, pleaded guilty on both charges. Having regard to his position, nominal fines only were imposed by the court.

THIRD WORLD CONGRESS ON FERTILITY AND STERILITY

The Third World Congress on Fertility and Sterility will be held in Amsterdam from June 7th to 13th, 1959. The themes of the Congress are:—

Embryonal death.

Hormonal factors and vitamins in fertility and sterility.

Relative value of the techniques for the study of the endocrine functions in human sterility.

Biochemistry of spermatogenesis, and

Psycho-sexological problems in sterility.

The registration fee is $40 for full members and $15 for associate members. Suggested titles for papers should be submitted to Dr. Alfonso Alvarez-Bravo in Mexico City 5, D.F., Mexico, or to Professor Dr. B. S. ten Berge, c/o Academic Hospital, Groningen, the Netherlands. For further information and registration, prospective participants should apply to the Secretariat of the Third World Congress on Fertility and Sterility, Secretariat, 4, Sint Agnietenstraat, Amsterdam-C., the Netherlands.

NEW LEGISLATION GOVERNING THE EXPORT OF PONIES AND HORSES

The Minister of Agriculture, Fisheries and Food and the Secretary of State for Scotland have jointly made Orders to protect ponies carried to destinations outside Europe by sea or air from unnecessary suffering during their journey.

The purpose of the Exported Ponies Protection Order is to ensure that no pony, apart from certain high-quality animals, is shipped by sea or air from Great Britain to any place outside Europe unless it has been inspected by a Veterinary Inspector immediately before going on board and certified as fit to be conveyed to its destination. This Order makes statutory the present informal arrangement whereby the shipping companies concerned have agreed to allow all the ponies which they ship to be inspected by a Veterinary Inspector of the Ministry or the Department of Agriculture for Scotland.

The Horses (Sea Transport) Amendment Order amends the Horses (Sea Transport) Order, 1952, in three respects: lighting in the parts of a ship in which horses are carried must be dimmed at night; the owner of a vessel carrying horses must provide a person experienced in the handling of horses to be responsible for their care; and all ships carrying horses must be provided with means of access to the horses carried below deck in addition to hatchways.

The Orders will come into operation on August 18th, 1958.

MAJOR W. F. JARRATT

Mr. G. N. Gould writes:—

During my recent tour of British Guiana I met Major W. F. Jarratt (whose death was announced in THE VETERINARY RECORD last week), in company with the small number of veterinary surgeons resident in, and working in, that country. His prestige among his colleagues was high and their appreciation of his work was shared by Mr. Colin Campbell, President of the British Guiana R.S.P.C.A., and his committee.

During a period of 3 years as veterinary surgeon to the R.S.P.C.A. Major Jarratt had developed an admirable clinic service for the use of the people of Georgetown, which had been increasingly used, and had made a magnificent contribution to animal welfare in a country in which such services are a pressing need. He had received great assistance from his very charming and capable wife who acted as secretary, dispenser, and surgical assistant.

I visited his clinic, which comprised a small waiting room, office, dispensary, and operating room, well organised, remarkably clean and tidy, but lacking in equipment which might be considered essential but for want of funds. Major Jarratt was using his own instruments, of which meticulous care was taken. There was an X-ray apparatus but no cassettes or films. The case records, however, showed a wide scope of professional services for small animals—donkeys in particular—and demonstrated how he had overcome many difficulties and frustrations.

Major Jarratt, in company with his colleagues, attended the daily discussion group organised during my visit and showed a keen and well-informed grasp of the prevailing agricultural and livestock problems. He had been offered, and had accepted, an appointment, at the termination of his 3 years with the R.S.P.C.A., as veterinary surgeon to one of the larger sugar estates—a post of considerable responsibility.

His concern for animal welfare and for his work for the R.S.P.C.A. were shown by his acceptance being made subject to being able to continue to provide his services for the clinic in an honorary part-time capacity pending the appointment of a successor. He asked me to make the R.S.P.C.A. in London aware of the needs of animal welfare in British Guiana, of the lack of financial support, and of the development that could ensue if such support were forthcoming for the benefit of animals.

I regret to say that, on my return to England, this approach met a lack of response which surprised me.

During the very few days that I was able to enjoy the friendship of Major and Mrs. Jarratt I was impressed with the way in which the prestige of the Royal College, and the service of its members to the community, was exemplified in his work in British Guiana.

The sympathy of all who knew Major Jarratt will be extended to Mrs. Jarratt in her sad bereavement.

MR. T. R. THOMAS

We regret to announce that Mr. Thomas Roger Thomas, of Carmarthen, has died at the age of 70. He was one of the pioneers of the Attested Herd scheme in West Wales and was responsible for the first T.T. herd in Wales, that of Mr. T. Rees, of King's Park, St. Clears. He played a great part in commending to farmers the benefits of attestation. Mr. Thomas was the first secretary, and later became President of the South Wales Division of the B.V.A.

UNIVERSITY NEWS

Liverpool

DEGREE OF B.V.SC.

Second Examination, Part III (Animal Management)

Arnott, J. N., Brown, M., Bush, B. M., Carter, D., Cotgreave, D. H., Davies, G. E. G., Dunton, J., Edwards, G. B., Giam, C. H., Harding, A. J., Horrocks, Susan, Kemble, P. R., Kennington, D. A., Littlewood, H. F., Llewellyn, G., Love-Jones, H., MacLean, C. W., Peel, D. R., Smith, B. J., Strawbridge, G. E., Waugh, I. R., Weinberg, R., Whittaker, J. F., Williams, G. V., and Williams, M. H.

PERSONAL

Mr. Austin Sullivan Brooksbanks of Southport, a retired veterinary surgeon, left £38,848 gross, £38,721 net (duty paid, £9,325). He left £250 to the National Spastics Society and £250 to the Victoria Veterinary Benevolent Fund.

Mr. Frank H. Garner has been appointed Principal of the Royal Agricultural College, Cirencester. He succeeds Professor Robert Boutflour, who has retired for health reasons after 27 years as Principal.

Mr. B. V. Jones has been appointed head of the veterinary research department of Allen & Hanburys Ltd.

Dr. R. F. Montgomerie will leave this country on September 4th for an extensive tour of veterinary research centres in the United States, Canada, Australia, and New Zealand. He expects to return on December 18th.

Births

BARR.—On July 27th, 1958, to Margaret, wife of Gordon Barr, B.V.M.S., M.R.C.V.S., of Allenby Road, St. Annes, Lancs., a son, Gordon Andrew Carmichael.

BETTS.—On August 3rd, 1958, to Joan, wife of Alan O. Betts, M.A., PH.D., B.SC., M.R.C.V.S., of 12, Southacre, Latham Road, Cambridge, a son, Philip Nigel.

CARTER.—On July 24th, 1958, to Valerie, wife of Henry E. Carter, M.R.C.V.S., of 565, Green Lane, Ilford, Essex, a son, Simon, brother for Susan.

POLLEY.—On August 2nd, 1958, to Kathleen, wife of Maurice J. Polley, M.R.C.V.S., of 22, London Road, Hailsham, Sussex, a son, Trevor Niall, a brother for Simon.

SMITHSON.—On August 6th, 1958, at Bedford General Hospital, to Margaret (*née* Smith), wife of T. Brian Smithson, M.R.C.V.S., a daughter (Julia Margaret), a sister for Martin.

Marriages

EZEBUIRO—JOHNSON.—On August 2nd, 1958, at the Register Office, St. Marylebone, London, W.1, by special licence, Emmanuel Ogoegbulam Ezebuiro, B.VET.MED., M.R.C.V.S., of Umuahia, Nigeria, to Violet May Johnson, S.R.N., D.T.N., of St. Mary, Jamaica.

LLEWELLYN—JEFFREYS.—On Saturday, July 12th, 1958, at St. Martin-in-the-Fields, London, Geoffrey G. Llewellyn, B.V.SC., M.R.C.V.S., of Peterborough, to Christina R. Jeffreys, B.A., of Bristol.

COMING EVENTS

September

3rd (Wed.). Meeting of the Southern Counties Veterinary Society at the Polygon Hotel, Southampton, 7.30 p.m.

17th (Wed.). Meeting of the North Wales Division at Glynllifon, Caernarvon.

21st to 26th (Official Opening, Monday, September 22nd). 76th Annual Congress of the British Veterinary Association in Douglas, Isle of Man.

ADDRESSES OF DISEASE INFECTED PREMISES

The list given below indicates, first the county in which are situated the premises on which disease has been confirmed, followed by the postal address and date of outbreak.

Foot-and-Mouth Disease

Merioneth. Llainwen, Trawsfynydd (Aug. 4).

Fowl Pest

Cambs. C.W.S. Farm, Stags Holt, March (Aug. 2); 114, West End, March (Aug. 5); 114, Wisbech Road, March (Aug. 6); 3, Prospect Road, March (Aug. 7).

Essex. Peartree Hall, Earls Colne, Colchester; 502, Ipswich Road, Colchester; Silver Spring Farm, Thorrington, Colchester (Aug. 5); Wyldberry Poultry Farm, Fox Street, Ardleigh, Colchester; Woodpeckers, St. Johns Road, Colchester (Aug. 6).

XUM

Norfolk. The Bungalow, Hall Corner, Hevingham; Bradcar Road, Shropham; Rifle Range, Catton Grove Road, Norwich; The Homestead, Hevingham (Aug. 1); London Restaurant, Church Street, Cromer (Aug. 2); Valley Farm, Holt Road, Hevingham; Hillside Caravan Site, Manor Road, Hunstanton (Aug. 3); Grange Farm, Shropham, Norwich (Aug. 4); Oak Tree Poultry Farm, Marsham (Aug. 5); Boundary Farm, Garlick Street, Pulham St. Mary, Diss (Aug. 6); 22, Trory Street, Norwich; Streamlet Farm, Starston, Harleston (Aug. 7).

Notts. 14, Princes Street, Eastwood (Aug. 7).

Surrey. Warren Farm, White Lane, Ash Vale (Aug. 3).

Sussex. Walnut Farm, Heathfield (Aug. 2); South Farm, Langton (Aug. 5).

Swine Fever

Beds. 12, Kensworth Road, Studham, Dunstable (Aug. 7).

Bucks. Upton Court Farm, Upton Court Road, Slough (Aug. 6).

Cambs. The Orchard, Mildenhall Road, Fordham (Aug. 5).

Derbys. Firbeck House Farm, Whitwell (Aug. 6).

Dorset. The Caravan, Holmwood Farm, Longham, Ferndown, Wimborne (Aug. 5); Piggeries, R.A.C. Centre, Bovington Camp, Wareham (Aug. 7).

Essex. The Allotments, Coopers Lane, Clacton-on-Sea; 46, St. Johns Road, Colchester (Aug. 5).

Hants. Watsons Farm, Sherfield English, Romsey (Aug. 7).

Lancs. Lakelands, Anderton, Chorley (Aug. 6).

Middx. The Cottage (Lower Farm), Harlington, Hayes (Aug. 6).

Norfolk. Low Farm, Stradbroke, Diss; Hall Farm, Wroxham (Aug. 1); Piggeries, The Poultry Farm, Stephens Road, Cromer; The Elms, Starston, Harleston (Aug. 6).

Suffolk. Foxes Farm, Battisford, Stowmarket (Aug. 1); Hall Farm, Debenham, Stowmarket; Long Lane Farm, Corton, Lowestoft; Well Farm, Witnesham, Ipswich; Silver Farm, Lawshall, Bury St. Edmunds (Aug. 5); Brick Kiln, Withersdale (Aug. 6).

Sussex. New House Farm, Willingdon Drove, Langney, Eastbourne (Aug. 5).

Letters to the Editor

The views expressed in letters addressed to the Editor represent the personal opinions of the writer only and their publication does not imply endorsement by the B.V.A.

SCIENTIFIC

Stillbirths in Cattle

Sir,—Over the last calving season there has been a noteworthy increase in the number of stillbirth outbreaks in cattle brought to the attention of the Veterinary Investigation Service. Loosmore, Shaw, Stevens, Brooksbank, and Hughes, have each independently brought evidence that a proportion of these outbreaks in all breeds may be associated with the "iodine deficiency" syndrome described by P. Hignett (1953), and Allcroft, Scarnell, and S. L. Hignett (1954). Koch (1952), however, attributed the characteristic features, such as poor yield, uterine inertia, and sluggish fatness to a varying congenital ability of the individual's thyroid to produce thyroxin, and Filsinger (1955) demonstrated that there could be a breed variation in the incidence of "hypothyroidism." Presumably, therefore, when temporary iodine deficiency occurs, it is apt to affect most herds of the more susceptible breeds, and the more susceptible

AN ANALYSIS OF STILLBIRTH OUTBREAKS

Herd	No. of cows	No. of still-births	No. 1st and 2nd calf dams	No. held clean-sings	Mean No. days pre-mature	No. of dams high yielding	Dams above average yields	Dams below average yields	Dams below average in flesh	Remarks
Mu. Guernsey	17	4–23·5 per cent.	2	4	21	3	1	–	2 or 3	2 dams were mother and daughter. High yield average rising over the years.
Ma. Jersey	50	5–10 per cent.	2	1	8	4 (highest in herd)	1	–	3	2 dams were grandmother and daughter.
W Jersey	50	5–10 per cent.	3	–	10·5	4	1 average	–	3	High yield average rising over the years.
D Jersey	11	5–45·5 per cent.	4	2	–	4	1 average	–	4	
U Shorthorn/ Jersey	52	7–13·5 per cent.	4	–	–	–	6 plus 1 average	–	– (but whole herd on poor side)	3 dams of same cow family. Other cows return at irregular intervals.
TOTALS	180 mostly Channel Island	26–14·5 per cent. mean	15–60 per cent. of dams involved	7–27 per cent.	6·3	15	8	Average 3	12–19	7 stillbirths in 3 herds involved closely related dams.
C Friesian	70	8	5	–	–	1	1	6–4 definitely poor	– (4 above average and 4 average)	Leucorrhoea and silent heats conspicuous. Enlarged thyroids palpable in 2 live calves.

individuals within herds. But in a series of 6 stillbirth outbreaks investigated in dairy herds this year by the writer, only one herd, "C," was found to show the features conforming to this pattern, including enlarged thyroids palpable in the living calves, and purulent endometritis in the affected and other cows.

As the Table shows, the remaining 5 herds, in marked contrast, showed features characteristic of *hyperthyroidism*, with a strong tendency to very high milk production and a low condition of flesh; 4 of the herds involved Jerseys and the fifth Guernseys, typically hyperthyroid breeds by Filsinger's criteria. McDonald, Nichols and McNutt (1954) demonstrated experimental production and prevention of retained placenta; the retention by withholding exogenous progesterone from the ovariectomised subjects after the 25th day before they were due to calve. A proportion of the resulting calves was non-viable and the gestation period was shortened to a mean of 268 days, about 10 to 14 days less than normal. McDonald considered that the same syndrome might occur in the field as a functional disease; Hays and McDonald (1957) confirmed these results; of 178 intact cows of which alternate individuals received supplementary progesterone during the last month of pregnancy, all the 5 control dams to produce twins did retain the placenta, while the 3 supplemented dams of twins cleansed normally.

Now from the data in the attached Table relative to the first "hyperthyroid" herd "Mu," it appears that McDonald's (1954) experimental syndrome may actually have been reproduced in the field as indeed he foresaw. At all events the placental retention so clearly evidenced is accompanied by a similar reduction in the duration of pregnancy, and it seems reasonable to expect some progesterone deficiency in hyperthyroidism, since the demands for this hormone by the udder might in this condition be much increased. The data from the herds (also hyperthyroid) Ma, W, D, and U, seem generally to support the hypothesis; there is also a suggestion of inheritance of the tendency towards this form of functional inadequacy—in accordance with Hanson's view (1956).

Prophylaxis against stillbirths in "hypothyroid" herds seems to demand supplementation with thyroid extract as well as iodine, while in the "hyperthyroid" herds it may be economic to treat with progesterone, cows with an hereditary or individual history that suggests their calves may otherwise be stillborn; though the risk appears less in calvings later than the second. Less than 200 mg., implanted 6 weeks and repeated 3 weeks before the due date, is unlikely to be effective.

Yours faithfully,
F. L. M. DAWSON,
A.V.I.O. (Sterility).
Ministry of Agriculture, Fisheries and Food,
Veterinary Investigation Centre,
Milton Road,
Cambridge.
July 24th, 1958.

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Roach Back and Disc Protrusions

Sir,—The possible factors predisposing a breed or individual dog to clinically significant protrusions of the intervertebral discs remain a fruitful field for speculation and investigation.

We have wondered if the actual conformation of the spinal column may play some part in creating abnormal stresses and strains in these structures in that kyphosis in the thoraco-lumbar region, *i.e.* roach back, has been present in many of our cases of disc protrusion. We wish to indicate a distinction between those breeds in which the whole thoracic and lumbar spine is normally curved as in the greyhound and whippet (breeds in which clinical evidence of disc protrusion is virtually absent) and those in which we regard the localised spinal curvature as being a fault of conformation, *e.g.* Pekingese and Dachshund.

In the discussion on Dr. King's paper, "The Anatomy of Disc Protrusion in the Dog" (*Vet. Rec.*, 1956), one of us (J. O. J.) asked the essayist for his views on the normal spinal curvature of the dog and the part played by roach back in clinical cases; the reply indicated that there were divided opinions on the subject of roach back *following* disc protrusions. We have speculated as to whether the existence of a roach back might predispose the individual to prolapse of the nucleus pulposus in certain cases. We have recently had the opportunity of making a *post-mortem* examination of a case we feel may be worthy of mention in this connexion.

The subject was a 9½-year-old Chow Chow bitch, Champion Mairim Chinky Miss; according to the owner she had "gone off her back legs" and euthanasia was being considered. Knowing that this bitch had from puppyhood had a quite distinct roach back, an abnormality of conformation decidedly uncommon in the Chow, permission was sought to carry out a *post mortem* when the owner's veterinary surgeon had destroyed the dog.

Mr. Hannaford, M.R.C.V.S., kindly supplied further details of history which extended over a period of 6 to 7 months prior to destruction; his observations indicated an increasing posterior paresis rather than a paraplegia as had been suggested by the owner's description.

Post-mortem examination carried out by one of us (D. M. M.) showed numerous disc protrusions, all of Hansen's Type II.

Post-mortem *Findings*

The cadaver was that of a bitch in good condition, with no signs of pressure sores or excessive wear of the hind toes as seen in true paraplegia. There was kyphosis in the thoraco-lumbar region, of a severe degree for this breed, extending from the 5th thoracic to the 4th lumbar vertebra with its highest point at the 10th/11th thoracic vertebrae. The spinal cord appeared to be normal macroscopically and there were no adhesions of the meninges to the spinal canal.

Protrusions of varying degrees were found at the following intervertebral spaces:—

7th cervical/1st thoracic: slight lateral projections each side of mid-line;

9th/10th thoracic: very slight ridge;

11th/12th thoracic and 13th thoracic/1st lumbar: slight ridges;

1st/2nd lumbar space showed a large protrusion across the entire width and about 2.5 mm. high. There were slightly smaller protrusions at each succeeding lumbar disc with the exception of the last, at the 7th lumbar/1st sacral space, which appeared normal.

None of the abnormal discs was herniated into the canal, and their contents were dry and fibrous.

The interest of this case lies in the fact that in the course of a very extensive experience of Chow Chows, both professionally and otherwise, no case can be called to mind in which symptoms ascribable to intervertebral disc protrusion have been seen; we wish to emphasise that we do not claim that Chows do not have disc protrusions since we have no evidence on this point; merely that they do not suffer from any of the syndromes now ascribed to this condition.

It seems to us that on the following counts the findings in this case do lend support to our tentative theory regarding roach backs and clinically significant disc protrusions:—

(a) Chows are a breed not prone to clinical disc protrusions.

(b) The bitch described above was known to have the abnormal conformation of a roach back throughout life.

(c) She displayed signs which are now recognised as being frequently associated with disc protrusions.

(d) *Post-mortem* examination showed the presence of numerous protrusions.

We feel it is not unreasonable to suggest that in this animal abnormal conformation predisposed her to clinically significant disc protrusions, which on breed grounds we should not have expected. It is but a single case and a small point in the mass of information now being accumulated, but we feel that anything which may lead to better understanding of the factors predisposing to disc syndromes is worth noting.

We are indebted to Mr. P. J. Hannaford for supplying the history and allowing us to have the body, and to the owner, Mrs. M. A. Simpson, for permitting this examination.

Yours faithfully,
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August 8th, 1958.

Reference

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GENERAL

New Mileage Allowance for L.V.I.s

Sir,—I wish to associate myself with those who protest against the imposition of this new scale. At the same time I would like to call attention to the injustice of the limiting of mileage allowance to 20 miles per journey which is imposed for most L.V.I. duties.

Some time ago I was in the company of an L.V.I. who was established in a town at the mouth of a glen or valley some 30 miles long. Scattered up this glen were a number of farms. Because of this situation the L.V.I., in the course of carrying out official tuberculin tests on behalf of the Ministry, would sometimes travel 80 miles in one journey. Despite the fact that no other veterinary surgeon could gain access to this glen without covering the same route the Ministry continued to insist upon their 20-mile limit. In other words, this L.V.I. is compelled to present the Ministry with 60 free miles each time he makes this journey. To make matters worse, when a member of the Ministry's whole-time staff makes precisely the same journey in his own car he is entitled to clock up every mile and the Ministry pays up without demur.

One need not leave the more densely populated areas to come across similar instances. It is quite possible for an L.V.I. while engaged upon official duties to cover considerably more than 20 miles without ever being more than 7 or 8 miles from his surgery.

Under the new scale of fees those who, in the past, have been unjustly penalised under the 20-mile limit will suffer even more because in calculating units of 1,000 miles the Ministry will take into account not actual miles but only allowable miles. Thus the long journeys which formerly have been only marginally economic will now become hopelessly uneconomic.

I can see in this arrangement a source of considerable worry for the unfortunately situated L.V.I. If he finds it uneconomic to perform these duties over these long distances it may well be that he dare not refuse to do them in case the Ministry adopt the attitude that if he is not prepared to do all then he may not do any.

Yours faithfully,
J. P. PICKERING.

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August 9th, 1958.